virus (HSV) comprising a modified HSV genome wherein said modification comprises a modification of an inverted repeat region of said HSV genome such that only one $\gamma_1$34.5 gene remains intact, said amount of HSV being effective to reduce tumor mass.

REMARKS

The specification is amended to identify all related U.S. applications, their relationships to the present application, and their current status. The previous priority information was incomplete in that it did not include the information of U.S. Application No. 09/244,748. Because this information is provided both later than four months from the filing of the present application and later than sixteen months from the filing of the prior application, Applicant files herewith a Petition for Acceptance of an Unintentionally Delayed Claim for Benefit of a Prior-Filed Application Under 35 U.S.C. § 120.

Claim 1 is amended herein to clarify that the modification alters the virus such that only one $\gamma_1$34.5 gene remains intact. Support for this amendment can be found throughout the specification, *e.g.*, page 4, line 12, to page 5, line 2; and page 7, lines 26-29. Claim 1 is also amended to correct a typographical error introduced into the claim in the previous amendment.

II. RESPONSE TO THE OFFICE ACTION OF OCTOBER 11, 2002

A. The Status of the Claims

Claims 1-9 are currently pending.

Claims 1-9 stand rejected.

Claim 1 is amended herewith.

B. The Outstanding Rejections

Claims 1-9 stand rejected as assertedly not enabled by the specification, as assertedly lacking written description, and for assertedly being indefinite.

C. Patentability Arguments

1. The Rejection for Lack of Enablement Should Be Withdrawn

The Office Action indicated that limiting the claims to the direct injection of the virus into tumors would obviate the enablement rejection. This limitation was deemed necessary because, assertedly, "[t]here is no evidence presented that systemic administration (or any

administration other than direct injection) would result in the reduction of tumor mass in any individual other than a nude mouse." (Office Action, page 3) Applicant submits herewith post-filing scientific articles corroborating Applicant's position that claims 1-9 are enabled by the specification.

Neither the claims nor the specification limit the claimed methods to any particular mode of administration. Applicants have maintained that the specification demonstrates an operative aspect of the invention against which all alternative aspects can be compared by routine optimization. The Examiner wishes the Applicant to amend the claims to the exemplified embodiment (intratumoral injection). The rejection questions the efficacy of other routes of administration of HSV.

As demonstrated in the present specification, Kooby et al. ("Kooby," Exhibit A) describe the effectiveness of HSV in infecting and killing non-neurological tumors. Kooby utilize G207, an HSV-1 virus lacking both copies of the $\gamma_1$34.5 gene. Using athymic rats containing human colorectal cancer tumors established from three different colorectal cell lines, Kooby demonstrate that direct injection of G207 suppressed tumor growth significantly (p. 1328, right column). Kooby also demonstrates that G207 is effective when administered **regionally**. Specifically, administration of the virus through the portal vein was effective in preventing metastatic nodules from appearing in the liver. Thus, Kooby provides evidence that HSV is effective at inhibiting the proliferation of colorectal tumor cells, in a non-mouse animal system, and by multiple modes of administration.

Walker et al. ("Walker," Exhibit B) further supports the proposition that HSV therapy is effective in treating non-neurological tumors through multiple modes of administration. Walker describes the use of G207 in reducing prostate adenocarcinoma tumor volume in a subcutaneous system in nude mice by direct injection of the virus into tumors (Fig. 2) and by **systemic** administration of the virus through the tail vein (Fig. 4).

The articles demonstrate that $\gamma_1$34.5(-) HSV therapy is effective when administrered through modes other than by direct injection in nude mice. Regionally and systemically administered virus are able to infect and destroy target tumor cells. Thus, there is no reasonable scientific basis for the position that viruses containing one intact copy of $\gamma_1$34.5 should not infect cells when administered regionally or systemically, as the G207 strain was administered. Thus, the cited articles provide the evidence requested by the Examiner showing "that systemic administration (or any administration other than direct injection)

would result in the reduction of tumor mass in any individual other than a nude mouse." Accordingly, Applicant respectfully submits that the rejection has been overcome and requests withdrawal of the rejection of claims 1-9 for lack of enablement.

2. The Rejection for Lack of Written Description Should Be Withdrawn

The claims are directed to methods of reducing tumor mass comprising the step of administering to an individual suffering from cancer an amount of a Herpes simplex virus (HSV) comprising a modified HSV genome comprising a modification of an inverted repeat region of the HSV genome such that only one $\gamma_1$34.5 gene remains intact and the amount of HSV being effective to reduce tumor mass. Wild-type HSV comprises two copies of the $\gamma_1$34.5 gene. The amendment to claim 1 further clarifies that the HSV genome modification is such that only one of the two $\gamma_1$34.5 genes remains intact. Thus, claim 1, as amended, does not include methods wherein HSV having more than one intact $\gamma_1$34.5 gene is administered, as suggested in the Office Action at pages 14-15.

The Patent Office's reliance on The Regents of the University of California v. Eli Lilly and Co., 119 F.3d 1559 (Fed. Cir. 1997) is misplaced. That case involved claims to a genus of compounds each having distinct structures (mammalian or vertebrate cDNA encoding the insulin polypeptide) that were known to exist. However, the specification only provided the structure of one such compound (rat cDNA encoding insulin). As noted in Fiers v. Revel, 984 F.2d 1164 (Fed. Cir. 1993), conception and reduction to practice of a DNA coding for a specific protein often occur simultaneously. This may be true when the particular DNA has a distinct chemical structure. Because the patentee had not described the structure of the compounds, but only their function, the Lilly court held that the specification did not provide a description of the genus of distinct compounds.

Here, the claims are not to compounds having a distinct structure. Rather, the claims are to methods. The methods utilize an HSV comprising a HSV genome modified such that only one $\gamma_1$34.5 gene remains intact. Applicants maintain that is irrelevant whether there are thousands if not millions of ways one could modify an HSV genome such that only one $\gamma_1$34.5 gene remains intact. The issue is whether Applicant was in possession of the invention drawn to methods of administering a modified HSV as of the effective filing date. Satisfaction of 35 U.S.C. § 112, first paragraph, requirement for an adequate description does not require a product specification for commercialization of each embodiment of the claimed

method. The written description requirement is satisfied if Applicant provides a description sufficient to allow one of ordinary skill to recognize that Applicant invented the methods as of the effective filing date. Applicant provides such a description. Applicant respectfully submits that the rejection of claims 1-9 under 35 U.S.C. § 112, first paragraph, for lack of written description has been overcome and respectfully requests withdrawal of the rejection.

3. The Rejections under §112, Second Paragraph

Applicant amends claim 1 herein to clarify that the modification is such that only one of the two $\gamma_1$34.5 genes remains intact and to correct "γ1.34.5" to correctly read " $\gamma_1$34.5." The clarification that only one $\gamma_1$34.5 gene remains intact clarifies the nature of the modification to the genome.

Regarding the clarity of "said amount of HSV being effective to reduce tumor mass," Applicant submits that the language is unambiguous and satisfies the definiteness requirement of 35 U.S.C. § 112, second paragraph. The language unambiguously defines the "amount" of the modified HSV that is administered as that in amount needed to reduce tumor mass.

Regarding the term "a unique region," Applicant clarifies that the use of the term, would be understood in the art, as referring to such distinct regions of the HSV genome as the long unique region and the short unique region. (See page 2 of Exhibit E of the previous Response). Applicant submits that this clarification renders moot the rejection of claim 5 under § 112, second paragraph.

For the reasons provided hereinabove, Applicant submits that the rejection of claims 1-9 under 35 U.S.C. § 112, second paragraph, has been overcome and should be withdrawn.

SUMMARY

For the foregoing reasons, each of the pending claims 1-9, as amended, is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejections of the claims and to pass this application to issue.

Dated: March 11, 2003

Respectfully submitted,

By _____

Thomas J. Wrona, Ph.D.
Registration No.: 44,410
MARSHALL, GERSTEIN & BORUN
233 S. Wacker Drive
6300 Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Attorneys for Applicant

VERSION SHOWING MARKED UP CHANGES

In the Specification

Replacing the text inserted before the first line by preliminary amendment on September 26, 2001 with the following:

--This is a Continuation of U.S. application Serial No. 09/629,021, filed July 31, 2000, now abandoned, which is a Continuation of U.S. application Serial No. 09/244,748, filed February 5, 1999, now abandoned.--

In the Claims

Please amend claim 1 as indicated below.

1. [Twice Amended] A method for reducing tumor mass comprising the step of administering to an individual suffering from cancer an amount of a Herpes simplex virus (HSV) comprising a modified HSV genome wherein said modification comprises a modification of an inverted repeat region of said HSV genome such that only one $\gamma_1$34.5 [γ1.34.5] gene remains intact, [and] said amount of HSV being effective to reduce tumor mass.